UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,639	10/29/2003	Maureen J. Bourner	PC27428	1858

28940 7590 01/13/2006

AGOURON PHARMACEUTICALS, INC.
10777 SCIENCE CENTER DRIVE
SAN DIEGO, CA 92121

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,639	BOURNER ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *9-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed November 17, 2005 in response to the Office Action of October 20, 2005 is acknowledged and has been entered. Applicant's election of Group I (claims 1-8) without traverse is acknowledged.

Claims 1-14 are pending. Claims 9-14 are withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-8 are currently under prosecution.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 1-8 are rejected under 35 U.S.C. 101 because the claimed invention, an antibody, is directed to non-statutory subject matter.

The claims read on an antibody that is found in nature. Products of nature do not constitute patentable subject matter as defined in 35 USC 101. See MPEP 2105. Since an antibody does not exist in nature in purified form, it is suggested that Applicant use the language "isolated" or "purified" in connection with the enzyme to identify a product that is found in nature.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 2, 3 and 6 rejected under 35 U.S.C. 102(b) as being anticipated by Shimoyama et al (J of Cell Biology, 1989, 109:1787-1794, IDS) (see sequence search Result 1 in PIR database).

The claims are drawn to an antibody that immunospecifically-binds to p-cadherin (claim 1), wherein p-cadherin has the amino acid sequence of SEQ ID NO:39 (claim 2), wherein the antibody is a monoclonal antibody (claim 3), wherein the antibody is an antagonist (claim 6).

Shimoyama et al teach a monoclonal antibody, NCC-CAD-299, that immunospecifically-binds to p-cadherin (p. 1788, col. 1), wherein p-cadherin has an amino acid sequence with 100% homology to SEQ ID NO:39 (see sequence search Result 1 in PIR database and Figure 3 of Shimoyama et al), and wherein the antibody acts as an antagonist by disrupting the cell-cell binding function of p-cadherin and dissociating cells that express p-cadherin (p. 1791, col. 2; 1792, col. 2; p. 1793, col. 1; Figure 9).

4. Claims 1, 2, 3, and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application 2003/0194406 (see sequence search Result 5 in the Published Applications database).

The claims are drawn to an antibody that immunospecifically-binds to p-cadherin (claim 1), wherein p-cadherin has the amino acid sequence of SEQ ID NO:39 (claim 2), wherein the antibody is a monoclonal antibody (claim 3), and wherein the antibody is an antagonist (claim 6).

US Patent Application 2003/0194406 teaches a monoclonal antibody, NCC-CAD-299, that immunospecifically-binds to p-cadherin ([0030]), wherein p-cadherin has an amino acid sequence, SEQ ID NO:1, with 100% homology to SEQ ID NO:39 of the instant application (see sequence search Result 5 in the Published Applications database; [0047]), and wherein the antibody is an antagonist that disrupts P-cadherin cell-cell adhesion ([0030-0031], Fig. 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 2, 3, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimoyama et al (J of Cell Biology, 1989, 109:1787-1794) in view of Francis et al (Int J Hematol, 1998, 68:1-18).

The claims are drawn to an antibody that immunospecifically-binds to p-cadherin (claim 1), wherein p-cadherin has the amino acid sequence of SEQ ID NO:39 (claim 2), wherein the antibody is a monoclonal antibody (claim 3), wherein the antibody is conjugated with polyethylene glycol (claim 5), and wherein the antibody is an antagonist (claim 6).

Shimoyama et al teach a mouse monoclonal antibody, NCC-CAD-299, that immunospecifically-binds to p-cadherin (p. 1788, col. 1), wherein p-cadherin has an amino acid sequence with 100% homology to SEQ ID NO:39 (see sequence search Result 1 in PIR database and Figure 3 of Shimoyama et al), and wherein the antibody acts as an antagonist by disrupting the cell-cell binding function of p-cadherin and dissociating cells that express p-cadherin (p. 1791, col. 2; 1792, col. 2; p. 1793, col. 1; Figure 9). Shimoyama et al does not teach the antibody is conjugated with polyethylene glycol.

Francis et al teach that polyethylene glycol (PEG) modification is a well-established technique and is one of the most important molecule altering structural chemistry techniques that is used to stabilize proteins (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the antibody taught by Shimoyama et al with polyethylene glycol because Francis et al teach that this practice is conventional or

well-known in the art. One would have been motivated to modify the antibody with polyethylene glycol in order to enhance protein stability.

6. Claims 1, 2, 3, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimoyama et al (J of Cell Biology, 1989, 109:1787-1794) in view of Riechmann et al (Nature, 1988, 332:323-327).

The claims are drawn to an antibody that immunospecifically-binds to p-cadherin (claim 1), wherein p-cadherin has the amino acid sequence of SEQ ID NO:39 (claim 2), wherein the antibody is a monoclonal antibody (claim 3), wherein the antibody is an antagonist (claim 6), and wherein the antibody is humanized (claim 7).

Shimoyama et al teach as set forth above. Additionally, Shimoyama et al teach the immunohistochemical expression of P-cadherin in carcinoma cells, the normal counterparts of which do not express P-cadherin (p. 1793, col. 2). Shimoyama et al does not teach the antibody is humanized.

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach that

"the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages over mouse antibodies. First the effector functions can be selected or tailored as desired...Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have humanized the mouse monoclonal antibody taught by Shimoyama et al by using the recombinant DNA techniques provided by Riechmann et al because the humanized antibodies would minimize an immune response against them which would have inhibited their activity. Further, one of ordinary skill in the art would have been motivated to genetically engineer or humanize the monoclonal antibody taught by Shimoyama et al in order to successfully localize antibodies to tumor cells for purposes of *in vivo* diagnosis because Shimoyama et al teaches that P-cadherin is expressed by carcinoma cells and not by their normal counterparts.

7. Claims 1, 2, 3, 4, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimoyama et al (J of Cell Biology, 1989, 109:1787-1794) in view of US Patent 5,001,225.

The claims are drawn to an antibody that immunospecifically-binds to p-cadherin (claim 1), wherein p-cadherin has the amino acid sequence of SEQ ID NO:39 (claim 2), wherein the antibody is a monoclonal antibody (claim 3), wherein the antibody is an antagonist (claim 6), and wherein the antibody is an antibody fragment (claim 4).

Shimoyama et al teach as set forth above. Additionally, Shimoyama et al teach the immunohistochemical expression of P-cadherin in carcinoma cells, the normal counterparts of which do not express P-cadherin (p. 1793, col. 2). Shimoyama et al does not teach an antibody fragment.

US Patent 5,001,225 teach that Fab and $F(ab')_2$ fragments lack the Fc fragment of an antibody, clear more rapidly from circulation and have less nonspecific tissue binding than intact antibody (col 9, lines 22-25) and further teach that Fab, F(ab')2 fragments may be used as well as the intact antibody in methods of detection and treatment (col 9, lines 26-32).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the antibody fragments taught by US Patent 5,001,225 for the antibody taught by Shimoyama et al by because the antibody fragments would have less nonspecific tissue binding than intact antibody. One of ordinary skill in the art would have been motivated to substitute the antibody with antibody fragments in order to successfully and more efficiently localize antibodies to tumor cells for purposes of diagnosis because Shimoyama et al teaches that P-cadherin is expressed by carcinoma cells and not by their normal counterparts.

8. Claims 1, 2, 3, 6, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimoyama et al (J of Cell Biology, 1989, 109:1787-1794) in view of WO 82/01461.

The claims are drawn to an antibody that immunospecifically-binds to p-cadherin (claim 1), wherein p-cadherin has the amino acid sequence of SEQ ID NO:39 (claim 2), wherein the antibody is a monoclonal antibody (claim 3), wherein the antibody is an antagonist (claim 6), and wherein the antibody is human (claim 8).

Shimoyama et al teach as set forth above. Additionally, Shimoyama et al teach the immunohistochemical expression of P-cadherin in carcinoma cells, the normal counterparts of which do not express P-cadherin (p. 1793, col. 2). Shimoyama et al does not teach an human antibody.

WO 82/01461 teaches that human monoclonal antibodies are useful for immunoassays (p. 2, line 36) and specifically teaches that hybridomas producing said monoclonal antibodies may be produced *in vitro* in the absence of *in vivo* immunization (p. 4, lines 34-40) and specifically teaches that subject human monoclonal antibodies find use in conventional applications for antibodies such as immunoassay, electrophoretic analysis, histology (p. 7, lines 22-28).

It would have been *prima facie* obvious to one of ordinary skill in the art to have produced human monoclonal antibodies of the antibody of Shimoyama et al because WO82/01461 specifically teaches that human monoclonal antibodies are easy to produce in that hybridomas for the antibodies may be produced *in vitro*, eliminating an *in vivo* step and because human monoclonal antibodies can be used for conventional

applications of all antibodies such as immunoassay, electrophoretic analysis, and histology. One of ordinary skill in the art would have been motivated to substitute the antibody with a human antibody in order to successfully localize antibodies to tumor cells for purposes of diagnosis because Shimoyama et al teaches that P-cadherin is expressed by carcinoma cells and not by their normal counterparts. One would have a reasonable expectation of success in producing human monoclonal antibodies given that the methods of making said human monoclonal antibodies were conventional in the art at the time the invention was made.

9. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Application 2003/0194406 (see sequence search Result 5 in the Published Applications database).

The claims are drawn to an antibody that immunospecifically-binds to p-cadherin (claim 1), wherein p-cadherin has the amino acid sequence of SEQ ID NO:39 (claim 2), wherein the antibody is a monoclonal antibody (claim 3), wherein the antibody is an antibody fragment (claim 4), wherein the antibody is conjugated with at least one polyethylene glycol moiety (claim 5), wherein the antibody is an antagonist (claim 6), wherein the antibody is humanized (claim 7), wherein the antibody is human (claim 8).

US Patent Application 2003/0194406 teaches a monoclonal antibody, NCC-CAD-299, that immunospecifically-binds to p-cadherin ([0030]), wherein p-cadherin has an amino acid sequence, SEQ ID NO:1, with 100% homology to SEQ ID NO:39 of the instant application (see sequence search Result 5 in the Published Applications

database; [0047]), and wherein the antibody is an antagonist ([0030-0031], Fig. 3, [0044], [0019-0134]). US Patent Application 2003/0194406 does not teach that the antibody is an antibody fragment, conjugated with polyethylene glycol, humanized, or is human.

US Patent Application 2003/0194406 teaches that P-cadherin antagonists include antibodies that will bind P-cadherin with greater affinity than other cadherins and that P-cadherin antagonists specifically include molecules that bind specific portions of P-cadherin ([0044-0045]). The reference teaches that antibodies include antibody fragments ([0034], [0091-0097], [0154-0155], [0155]), antibodies conjugated with polyethylene glycol ([0175]), humanized antibodies ([0102-0103], [0148-0151]), and human antibodies ([0152-0153]). The reference teaches that various techniques of producing antibody fragments are known ([0155]), and that methods of humanizing non-human antibodies have been described in the art ([0149]) and the production of human antibodies is known ([0153]), meaning these techniques are well known in the art.

Given the teaching that antibodies are antagonists and antagonists include molecules that bind to P-cadherin, and given the conventional antibody molecule forms of antibody fragments, antibodies conjugate to polyethylene glycol, humanized and human antibodies disclosed, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make the antibody of claim 1 in any of the conventional forms disclosed. One would have been motivated to make said antibody molecule forms with a reasonable expectation of success because of their conventional nature.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER